(12) INTERNATIONAL PATENT APPLICATION PUBLISHED IN ACCORDANCE WITH THE AGREEMENT ON INTERNATIONAL COOPERATION IN THE AREA OF PATENTS (PCT)

(19) WORLD PATENT ORGANIZATION
International Office

(43) International publication date:
April 10 3002 (04/10/2003) PCT

(10) International Publication No.:
WO 03/028698 A2

(51) International Patent Classification:
A61K 9/00

(21) International Appl. No.: PCT/EP02/10743

(22) International Appl. Date:
September 25 20021 (09/25/2002)

(25) Language of application: German

(26) Publication language: German

(30) Priority data:
101 47 414.8 September 26 2001 (09/25/2001 DE

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(81) Contracting states (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, DM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ. TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated states (*regional*): ARIPO-Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European Patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI-Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
- *without International Search Report and to be re-published on receipt of the Report.*

With regard to the 2-letter codes and other abbreviations refer to "Explanatory notes concerning codes and abbreviations" shown at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** METHOD AND DEVICE FOR PRODUCING GRANULATES THAT COMPRISE AT LEAST ONE PHARMACEUTICAL ACTIVE SUBSTANCE.

(57) **Abstract:** The invention relates to a method for producing granulates that comprise at least one pharmaceutical active substance according to which the powder to be granulated is introduced into an extruder. A granulated material is formed by adding granulating liquid and is compacted by transverse forces. A gas or a gas mixture can be optionally introduced into the compacted granulated material in order to render the granulated material porous.

WO 03/028698

Method and Device for Producing Granulates that Comprise at Least One Pharmaceutical Active Substance

The present invention relates to a method for producing granulates comprising at least one pharmaceutical active substance, a device for the production of such granulates, and the granulates produced by this method and device.

Granulation is understood to mean the conversion of powder particles into granulate grains, which is important above all for the fabrication of medicinal forms in the pharmaceutical industry but also for the fertilizer industry and the plastics industry. In the pharmaceutical area, granulates are used on one hand as independent medicinal forms that can be swallowed better in comparison to powder mixtures, and on the other as an intermediate product for the filling of medicinal capsules and for tabletting, whereby with a decrease in the surface of the powder mixture better flowing bulk materials are obtained, which can be compressed into mechanically more solid compressed items compared with powders. Granulates generally display the advantages of a defined bulk and flow behavior, diminished tendency to de-mixing and better wettability of the active and adjuvant substances.

Granulation takes place by a dry route, but mostly by a moist route. With moist-produced granulates, a distinction can be made between cake granulates, in which a formation of solid state bridges between the powder particles occurs due to crystallization of partly dissolved powder components, or as a solution of added adjuvants after evaporation of the granulation fluid, adhesive granulates in which binder bridges are formed by wetting mostly macromolecular substances with solutions, and also sinter granulates, in which bridges of solid substance are formed by the melting and subsequent solidification of components of the powder mixture.

In the pharmaceutical area, for the (moist) granulation, the intensive mixer and fluidized bed apparatus known to one skilled in this field are used almost exclusively. The quality parameters for the granulates produced by these methods are above all the particle size or their distribution, the particle porosity and the homogeneous distribution of material. All three parameters result in the methods cited from the choice of equipment and the choice of raw materials and are only in an extremely limited manner to be changed by the operating conditions. Of particular importance for the processing of granulates to tablets is the porosity of the granulates, which influences both the tablettability and also the later release of the active substance from the granulates or the tablets produced from

them. The porosity of granulates can be influenced very little by means of previously known granulation methods.

Another problem in moist granulation occurs with the granulation of hydrophobic active substances which can barely be wetted by aqueous fluids during the granulation. A homogeneous distribution of substances can in this case only be achieved by means of a good binder distribution, for which considerably higher energy input or considerably higher quantities of fluid are required.

Another problem is presented by the combined intermittent (batch-wise) operations in the two above—mentioned methods. This procedure conceals on one hand a great risk of non-homogeneities between the charges and thereby requires a high expenditure for control. On the other hand, it can bring with it difficulties in scale-up such that, due to the increasing size of the granulator and, if need be, changed geometry, a change in the behavior of the granulation mixture results, and thereby also a changed behavior of the resulting granulates.

It would therefore be desirable to have available a method for the production of pharmaceutical granulates that makes possible an intensive mixing of the mixtures to be granulated and/or the production of granulates with a desired, predefined porosity.

Such a method and a device for its execution are defined by the independent claims according to the present application. The dependent claims define advantageous forms of execution of the method and of the device in accordance with the invention.

Surprisingly, it has been found that, by using a specially modified extrusion unit, granulates comprising at least one pharmaceutical active substance can be produced by a method in which in particular the homogeneous distribution of substances can be improved by an energy input that can be adjusted over a wide range and in which the porosity of the granulate particles can be adjusted in a targeted manner by way of a targeted gas input and subsequent expansion. The method in accordance with the invention for production of granulates includes in principle the feeding of the powder or powder mixture to be granulated into an extruder, the addition of granulation fluid for the formation of a granulation mass and the compacting of the granulation mass in the extruder. Other common process steps can be connected in after this procedure, such as screening, drying, admixture of other components and the like. According to a particularly preferred form of execution of the invention method, after the compacting of the granulation mass in the extruder, a gas or

gaseous mixture is passed into the granulation mass to impart porosity to the granulation mass.

Extrusion units have been used up to now in the pharmaceutical field only in melting processes, in particular for the processing or treatment of fats, waxes or polymers and also in the production of pellets. In these kinds of extrusion methods, the masses to be processed in the extruder have completely different properties than the granulation masses to be processed in accordance with the present method. The method in accordance with the invention can be carried out with the use of extrusion units that are in themselves conventional but are modified so that they include a device for the dosaging of the powdered starting material to be granulated and also, in the case of the moist granulation method in accordance with the invention, a device for the dosaging of the fluid necessary to the granulation. According to a particularly preferred form of execution of the invention method, a gas is passed into the granulation mass in order to impart porosity to the granulation mass; in this case, the extruder also comprises an appropriate device for the passing-in of the gas as well as for the dosaging of the gas pressure and the amount of gas. Suitable extrusion units for the performance of the invention method are illustrated in the attached figures, which show:

Fig. 1: a schematic representation of an invention extrusion unit according to a first form of execution, in which there is no introduction of gas into the granulation mass;

Fig. 2: a schematic representation of an invention extrusion unit in accordance with a second form of execution, in which there is introduction of gas into the granulation mass;

Fig. 3: a schematic representation of an invention extrusion unit in accordance with a third form of execution of the invention with cellular wheel charging valves for dosage of the powder;

Fig. 4: a drawing of an invention two-stage extrusion unit in accordance with a particularly preferred form of execution, in which an introduction of gas into the granulation mass can occur, and

Fig. 5: a drawing of an invention single-stage extrusion unit in accordance with a particularly preferred form of execution, in which no introduction of gas into the granulation mass occurs.

As is shown diagrammatically in Figs. 1-3, the device for execution of the invention method basically comprises an extruder (D), a device for the dosaging of solid substances (A) and, optionally, a device for the dosaging of granulation fluid (B) and a device for the dosaging of gas (C). In the figures, (E) means process steps connected later, that is, processes that are usually subsequent to the granulation, such as for example screening, drying and mixing-in of other components. The type and extent of these later-connected process steps depend on the requirements and the later use of the granulate. For example, by pressure screening, granulate grains of an essentially uniform desired size can be obtained.

In the device for solid dosaging indicated in the figures by (A), a gravimetric metering screw or other suitable apparatus can be involved, that make possible a defined feeding-in of the powdered starting material of the granulate. The outlet from the metering installation opens on to the feed screw of an extruder or, if present, into its filling hopper. According to the form of execution shown in Fig. 3, instead of the filling hopper usually used for delivery of powder, a cellular wheel charging valve is used.

The device for fluid metering (B) serves to introduce into the process the fluid needed for the granulation, if need be also an adhesive solution, by way of a suitable injection device. The feeding point is preferably directly behind the feed screw in the forward region of the extrusion unit. Advantageously, it should make possible the recording of the quantity processed. The structure and type of dosage unit depends largely on the pressure ratios inside the extruder at this point and on the properties of the granulation fluid, such as viscosity, adhesiveness, etc.

In the extruder (D), the components added are processed to give an adhesive granulate or other processable mass. The extruder must transmit a minimum of transverse forces to the mixture in order to achieve an adequate dispersability. In order to make a specific dosaging of the components possible, certain pressure ratios must moreover prevail within the extruder, especially for the form of execution in which a gas is also introduced into the granulation mass in order to impart porosity to the granulation mass. The pressure ratios in the extruder are indicated by the wedges under the figures. Between the points designated by (1) and (2) (see Fig. 2), a pressure gradient must be created with increasing pressure in the direction of point (2), in order on one hand to raise the dispersion of the mixture, on the other hand however also to prevent a back-flow of the gas that is added directly behind the site with the highest pressure at point (2). It also results from this that directly in front of the addition point there must be a gas

density sealing of the extruder with material. Directly behind this, the mass pressure must again be low, to make possible the feeding-in of gas. Towards the end of the extrusion section the mass pressure naturally rises again, since a nozzle or other suitable molding unit is provided there, to avoid an emission of unprocessed gas and to increase the contact time between granulation mass and gas. Advantageously, the extruder can be cooled so that extrusion below the critical temperatures for the raw materials is possible. Advantageously, the rotation speed of the extruder and the extruder output are measured by means of suitable devices.

In the case of a particularly preferred form of execution, a gas, preferably nitrogen, is introduced into the granulation mass formed in the extruder to impart porosity to the granulation mass. In this form of execution, a device for dosaging the gas (C) is necessary, by means of which the gas is introduced into the process. Both the gas pressure and the quantity of gas can advantageously be regulated by means of appropriate apparatus such as pressure-reducers or volume flow meters. The maximum gas pressure required depends on the mass pressure of the mixture within the extruder at the point of feeding in of the gas as well as immediately in front of it and at the nozzle of the extruder. The measurement range of the volume flow meter depends on the throughput of the extruder and the desired porosity. Nitrogen is suitable as the gas, but any other gas is conceivable that does not adversely affect the quality of the product and is justifiable on other non-process-related grounds, in particular from the viewpoint of environmental compatibility.

Depending on the specifications of the raw materials and the requirements for the product, the devices shown in Figs. 1 and 3 can also be used.

In Fig. 1, a one-stage extrusion unit is shown in diagram form, in which the operation occurs without the introduction of gas and in previously mentioned pressure gradients. This configuration is advantageous for very pressure/shear-sensitive mixtures, the granulation of which, even without gas dispersion, leads to a product with adequate properties.

In Fig. 3, a device is shown diagrammatically in which instead of the filling hopper usually used for powder feed/delivery, a cellular wheel charging valve is used. The feeding of gas into the granulation mass can then occur, in spite of the one-stage construction, between the cellular wheel charging valve and the feed screw of the extruder. In order to prevent the exit of nitrogen in the product side of the extruder, either a nozzle can be used that prevents an exit of the gas by means of an appropriate seal, or, if a nozzle is to be dispensed with, instead

of the latter another cellular wheel charging valve can be integrated there. Depending on the material properties and the requirements set, with simultaneous use of a nozzle and a second cellular wheel charging valve, an equalization of pressure between the region of the feed screw and the region immediately behind the nozzle must be provided.

With the use of one of the above-discussed devices the production in accordance with the invention of a granulate takes place, by the powder or powder mixture to be granulated being brought by way of the dosaging unit (A) into the extruder. For the extruder, according to a particularly preferred form of execution, a planetary roll extruder is involved. A granulation mass is then produced in the extruder, either by feeding in a suitable granulation fluid such as water, ethanol, isopropanol or the like, or mixtures of the latter, or by feeding in a solution of suitable adhesives such as for example polyvidone, gelatin, cellulose derivatives and the like. The above-mentioned granulation fluids and adhesives are given only as examples of numerous other substances that are familiar to one skilled in the art. After optional gas input into the granulation mass, the latter exits from the extruder as a mass of cake-mixture consistency and can subsequently be processed further; it can for example be screened, dried and/or mixed with other components. The granulate so produced can then be used directly as the final medicinal form or it can be loaded into capsules or compressed into tablets.

The granulation unit of the particularly preferred planetary roll extruder consists of an obliquely toothed central spindle (4) that as the sole process part is connected directly with the drive and is mounted only at the drive site. Around the central spindle are arranged 3 to 7 planetary spindles (5) that display an opposite toothing and interlace to a large extent with the toothing of the central spindle. The planetary spindles in turn are mounted to the outside in the toothing of the casing (6). In this way, this system, considered from the front, displays great similarity to a planetary gearing.

The dispersion of the components is contrived by means of permanent rollers between planetary spindles and central spindle on one hand and by means of planetary spindles and casing on the other. These surfaces can preferably be tempered so that the process heat that appears is dissipated directly at the site of its origin, which permits excellent temperature control. The overall structure of the granulation unit is to be seen in Fig. 4. The granulation system shown in Fig. 4 has a two-stage structure, i.e. there are two more or less independent process steps of the above-described structure that are connected together only by a slot of a few millimeters width, formed of a butting ring and the central spindle. Thus

there is the possibility here of dosaging gas in between the first and second process part, so as to be able to further influence the product properties with respect to porosity. The gas is incorporated within the bounds of the possibilities of the goods to be extruded and effectuates an increase in the porosity of the product. Of course, another fluid can also be dosaged in at this site.

There is also the possibility of constructing a one-stage granulation system, as shown in Fig. 5. This is achieved by omitting the first granulation step and therefore also the middle butting ring, which in turn excludes an input of gas, for example nitrogen, into the granulate mixture. The properties of the granulate are not significantly changed by this compared with the two-step process, as long as the two-step comparison process is likewise run without gas.

The invention will be described further by means of the following non-limiting examples.

Methods:

Granulation unit

Analogously to the usual process steps in the granulation in the intensive mixer, weighing, granulation, drying and screening take place in sequence. Continuous operation requires a close meshing of powder or fluid dosaging and the granulation unit, whereas the subsequent process steps can follow separately from each other not only spatially but also with regard to time.

Granulation

The granulation unit was composed of a specially modified planetary roll extruder (L-WE 50, Entex Rust + Mitschke GmbH, Bochum, Germany) with a one- or two-step construction and a length/diameter ratio (LD) of 8 or 16. The powder mixture arrived in the extrusion or granulation region by way of a feed screw of length 4D, where the granulation fluid was added by way of an injection channel. In the two-stage construction it was moreover possible after 8D to bring gas into the system by way of a special butting ring. Moreover, by material sealing the ring prevented the flowing in of the gas opposite the direction of extrusion. The outlet opening of the extruder gave a tubular extrudate with a wall thickness of 1.5 mm and a diameter of about 30 mm.

Powder dosaging took place by means of a single-screw meter (Brabender, Duisburg, Germany), the granulation fluid was supplied by a peristaltic pump (Ismatec,

Zurich, Switzerland). Nitrogen was used as the gas in the two-stage construction. The entire granulation unit was cooled with water.

Drying

The drying of the granulated mass was carried out in the vacuum drying cabinet at 30°C. A continuously operating microwave-based dryer can however also be used.

Screening

All granulation extrudates were screened after the drying in the BTS 100 (L.B.Bohle Maschinen und Verfahren, Ennigerloh, Germany) (mesh bottom 1.0 mm grater screen, agitator blade sheet metal construction, 1500 rpm).

Measurement of porosity

The determination of the porosity of the granulation extrudate took place by way of the ratio of true volume to apparent volume. The true volume was measured in the gas pycnometer. The apparent volume was determined by coating the sample with a non-gas-permeable lacquer of known density, and the buoyancy of the sample thus prepared was determined in silicone oil of known density. On the assumption that the lacquer remains only on the surface of the sample and has no air inclusions, the apparent volume is given as:

$$V_S = \frac{m_P - m_S}{\rho_S} - \frac{m_L}{\rho_L} \qquad \text{Eq. (1)}$$

in which m_P is the mass, ρ_P the true density of the sample, m_L the true density, ρ_L the true density of the lacquer, m_S the reported weight in silicone oil and ρ_S the density of the silicone oil.

Thus the porosity ε is:

$$\varepsilon = 1 - \frac{\rho_P}{m_P V_S} \qquad \text{Eq. (2)}$$

Production of granulate

All solid substance components were dosaged as a pre-mix in the feed device. The granulation took place only with water.

To find the parameters of the granulation unit, first, at greatly increased water feed, ca. 50% of the maximum permissible powder feed was determined and then the amount of water was limited to a proportion determined by product temperature and power input. The product temperature should not exceed 60°C and the power input should be maximally 80% of the highest limit permissible. The rotational speed of

the granulator was set at 150 or 200 rpm. The drying of the product then took place to give a residual humidity of about 2.5%.

Testing of the granulates

The granulates were in addition characterized by flow rate, bulk and tamped density and Hausner factor. The flow rate was determined with the aid of a round discharge hopper with an aperture width of 11 mm, and the bulk and tamped densities in accordance with Ph. Eur.

Production of tablets

The granulates were mixed in the Turbulamixer (T2C, Willy A. Bachofen, Basel, Switzerland) at 90 rpm with the addition of disintegration accelerators and flow regulating agents or lubricants for 10 or 2 minutes. The granulate mass was 400 g, the volume of the mixing vessel 1250 ml. The compression of the final mixture took place on an instrumented eccentric press with a biconcave gang of punches; the rated mass was 400-430 mg.

Testing of the tablets

The construction of a compression force-breaking strength (tensile strength) profile took place at compression forces in the range of 6-18 kN. The tablets were also tested with respect to disintegration time and release of active substance. This was carried out with tablets of tensile strength 100 N, independently of the compression force used.

Equipment

Analytical balance BP 150 and *drying balance* (Sartorius, Gottingen, Germany), eccentric press Korsch EKO (Korsch, Berlin, Germany) with gang of punches 10 mm biconcave with embossing (Ritter, Hamburg, Germany), tensile strength tester (Schleuniger, Solothurn, Switzerland), disintegration tester ZT 6 (Erweka, Heusenstamm, Germany), Ultrapyknometer® 1000 (Quantachrome, Odelzhausen, Germany), scanning electron microscope Hitachi S 2460 (Nissei Sangyo, Ratingen, Germany).

Examples of Tests:

Granulation of poorly wettable active substances

The following tests were carried out without gas input. Three different poorly wettable substances were processed in high concentration with small amounts of polyvidone. The substances of the end mixture were added to the weighed quantity of dried granulate with the exception of magnesium stearate and mixed for 5 minutes

in the Turbulamixer at 90 rpm. Then the admixture of the lubricant took place for 2 minutes. The percentage fractions of the end mixture are reported as fractions of the total mass of the granulate mixture.

Formulation I

Granulate	Caffeine, anhydrous	97.5%
	Polyvidone	2.5%
End mixture	Polyvidone, crosslinked	3.0%
	Magnesium stearate	1.0%
	Silicon dioxide	0.5%

Caffeine is relatively non-critical for the granulation, because it is stable up to very high temperatures. Granulation could be effectuated starting from a water quantity of 8%. The granulation was carried out at 12% water addition and a resulting product temperature of 51°C.

The granulate flowed very well at 10 g/s and could be tabletted with no problems at a residual moisture of 1.4%, as shown by the compression force-tensile strength profile (Fig. 6).

The disintegration time was very short, 8 minutes immediately after the tabletting; the release profile of these tablets is shown in Fig. 7. The tablets had an extreme tendency to age, however. After storage for only two weeks, the release time had lengthened by almost 60-fold: the disintegration time rose to 56 minutes. Therefore a possibility had to be found for stopping or at least diminishing this aging. This problem could be solved by adding 5% cellulose. In this way, a disturbance of the granulate structure could be brought about that reliably stopped aging. The tabletting and release behavior were almost identical with that already reported. The technical stability could be confirmed analytically up to a storage period of six months. Testing after this period of time was no longer carried out.

An almost identically structured granulate was prepared on the basis of ibuprofen.

Formulation II

Granulate	Ibuprofen	92.0%
	Cellulose	5.0%
	Polyvidone	3.0%
End mixture	Polyvidone, cross-linked	3.0%
	Magnesium stearate	0.5%
	Silicon dioxide	0.5%

Ibuprofen has a relatively low melting point of 75-78°C, so that a maximum permissible product temperature of 40°C was set.

The granulation required 14% water and took place in a completely stable manner over a test period of 4 hours. The good flowability of the granulate could be confirmed, as could the easy tablettability. The residual humidity of the granulate before production of the end mixture was 1.4%. The release profile could also be confirmed as could the stability of the medicinal form over 6 months. The disintegration time was 1.7 seconds, which is not surprising because of the poor solubility of the active substance in water.

For a direct comparison, mefenamic acid was granulated with the addition of the identical adjuvants.

Formulation III

Granulate	Mefenamic acid	92.0%
	Cellulose	5.0%
	Polyvidone	3.0%
End mixture	Polyvidone, cross-linked	3.0%
	Magnesium stearate	0.5%
	Silicon dioxide	0.5%

Mefenamic acid is an almost unwettable active substance. Nevertheless, an almost complete coating of the active substance, analogous to Formulation II, was to be seen. The granulation, because of the poor wettability, required considerably more water. With a water addition of 22%, product temperatures of 75°C had been measured, which posed no risk for mefenamic acid, however.

The granulate was all in all finer than for Formulation II: due to the drying, fine fissures had resulted between active substance and binder, so that the mefenamic acid crystals were embedded in the binder residue more loosely and thus the extrudate was considerably more brittle. Nevertheless, drying to a residual moisture of 1.1% was possible with no problem.

Lower tablet stability and more extended release than for Formulation II were established; they are however attributable to the lower wettability or lower solubility of the mefenamic acid compared with ibuprofen as well as their different physical properties.

It could thus be shown that the proposed system is suitable for the granulation of formulations of very different types.

Granulation with the addition of nitrogen

In Table 1, formulations are shown that were granulated with nitrogen passed in. The components of the outer phase are percentage fractions of the granulate mass. All data in % (m/m).

Table 1

	IV	V	VI	VII	VIII	IX
Granulate						
Caffeine, anhydrous						
Lactose monohydrate	82.5	80.0	70.0	82.0		
Mannitol					72.0	80.0
Corn starch	14.6	15.0	15.0	5.0	10.0	
Cellulose			15.0	10.0	15.0	15.0
Polyvidone	2.9			3.0	3.0	
HPMC						5.0
Polyvidone, cl*		5.0				
Outer phase						
Magnesium stearate	0.5	0.5	0.5	0.5	1.0	1.0
Silicon dioxide, fine-grained						
Polyvidone cl*	5.0	2.0	5.0		5.0	5.0
Carboxymethylcellulose cl*				3.0		

*cross-linked

Formulation IV gave a moist granulate that could be foamed with no problem depending on the viscosity of the product. As expected, this can be controlled by way of the amount of water added. The smaller the quantity of water, the higher the viscosity, and the better the gas can be incorporated. The porosity of the granulate extrudate as a function of the gas pressure is shown in Fig. 8.

The overall porosity of the mixture appears to be very low in comparison to existing data on granulates in the literature, but it is to be taken into consideration that the porosity of a granulate extrudate is involved here, and that it is determined here quite differently from the porosity of a crude ore, which is usually given by the ratio of true density to tamped density and thus includes the interparticular spaces. This is given in the present granulate extrudates, however, only by the screening.

The porosity of the mixture rises with the gas pressure, since the pressure difference between gas pressure and mass pressure of the mixture decreases immediately in front of the outlet aperture of the granulation unit, and thus transportation of the disperse system through the outlet channel is made easier. The drop in the porosity at a gas pressure of 10 bar is to be explained by the fact that the gas exits in a more or less uncontrolled manner and is thus no longer available for rising the porosity. Here, the upper limit of the gas content of the system is reached that results from the mass pressure and the "density" of the granulate mixture and the cross-sectional area of the outlet aperture. Since directly in front of the gas entry channel the cross-sectional area of the granulation unit is lower than at the outlet aperture, a penetration of gas opposite the direction of extrusion is avoided.

The residual water content of the granulate extrudate immediately after granulation is about 10%, the product temperature decreases with increasing gas pressure (from 56°C to 50°C). As expected, the product temperature correlates primarily with amount of water introduced.

Due to the thus adjustable porosity, there was an influence on the tensile strengths. This is shown in Fig. 9; the compression force is 5, 10 or 15 kN. Clearly recognizable is an increase in the tensile strengths, which does not however, as would have been expected, increase with rising porosity, but drops again starting from a gas pressure of 4-6 bar. An explanation for this might be that with increasing gas pressure the number of cavities created by nitrogen within the granulate grains increases. Inside the latter, in the electron microscope,

almost unwetted powder fractions can be seen which can then be responsible for the worsening tablet properties.

The disintegration time of the tablets was 10-12 minutes for a tensile strength of 100 N, with the value being completely independent of the gas pressure used and correlating mainly with the tensile strength.

The other parameters of the granulates are to be seen in Table 2:

Table 2

Gas pressure (bar)	0	2	4	6	8	10
Bulk density (g/cm^3)	0.65	0.63	0.63	0.61	0.60	0.58
Tamped density (g/cm^3)	0.77	0.75	0.70	0.72	0.69	0.69
Hausner factor	1.189	1.179	1.108	1.184	1.143	1.195
Flow rate (g/s)	9.46	10.73	9.48	10.10	10.16	10.17

In the case of Formulation V, the parameters and in particular the disintegration times are largely in the range of Formulation IV at 0 bar. Thus the addition of cross-linked povidone in this granulation system brought no advantage for the disintegration time.

Formulation VI showed clearly shorter disintegration times of 6.5 minutes, which was to be expected because of the high cellulose fraction of 15%. This mixture, however, required about double the amount of water compared with Formulation IV. A change in the powder fraction used, with the water addition remaining the same, gave an influence on the compression force-tensile strength profile and, as expected, the product temperature. The disintegration time remained almost unaffected.

From these viewpoints, Formulation VII afforded a granulate with satisfactory tabletting and disintegration properties as well as an adequate gas retention capacity.

Formulations VIII and IX illustrate the use of other fillers and binders. However, a different effect was shown here than for the preceding formulations. In Formulation VIII, with increasing gas pressure, at first a decrease in tablet hardness was shown, but at 6 bar it rose again.

In Formulation IX, after an initial drop in the tabletting properties the expected increase in the tensile strength with rising gas pressure was displayed. The disintegration time, however, was considerably shorter, as was to be expected.

Thus it could be shown that the injection of nitrogen during the granulation had an effect on the tablettability of the granulates.

Moreover, the extent to which the nitrogen pressure had an effect on the properties of the granulates and tablets was investigated. For this, two ibuprofen mixtures were chosen, with combinations of HPMC and cellulose or amylo corn starch being used as adjuvants. In each case, 4% binder and 8% disintegration agent were added and acted on by 1.5 or 3.0 bar nitrogen. As reference, an identical granulate was prepared without the addition of nitrogen. The ibuprofen batch used (IBU) was IB1J584, BASF, Ludwigshafen. With addition of gas at over 3 bar, the sealing limit of the mass to be granulated was exceeded.

As shown in Table 3, strong effects on the disintegration and release behavior were determined:

Table 3

	IBU + HPMC + cellulose		
Nitrogen pressure	none	1.5 bar	3.0 bar
Disintegration time (min)	33.0	47.9	61.6
MDT (min)	20.71	34.43	46.61

	IBU + HPMC + starch		
Nitrogen pressure	none	1.5 bar	3.0 bar
Disintegration time (min)	17.9	45.2	52.2
MDT (min)	25.6	27.4	31.6

It is astonishing that the disintegration time was in part considerably greater than the reported mean dissolution time (MDT), which resulted from a gradual dissolution of the medicinal form without prior complete disintegration. The reasons for these effects were supplied by the scanning electron microscopic images, which with rising gas pressure reveal on one hand an increase in the number and size of the recognizable gas cavities, which in turn makes the porosity measurements appear less plausible. On the other hand, however, it could also be seen that inside the cavities there were almost unwetted particles of active substance. At first, this seemed improbable, since on passing the middle butting ring and thus before the entry of the nitrogen, the granulation had already ended and the particles of active substance must have been coated with binder. However, with the ibuprofen used here, a strongly lipophilic substance is involved, which

could thus enter in the interaction earlier with the non-polar gas than with the hydrophilic binder, whereby the nitrogen was put in a position to displace the HPMC used from the active substance.

This has far-reaching consequences for the gas addition which thus for this type of granulation is definitively disadvantageous in the production of rapidly disintegrating tablets. Nevertheless, there is a capacity to influence the release of active substance, without significantly changing or prolonging the tablettability, so that the addition of nitrogen should not generally be considered to be of no interest. Rather, an instrument is given here with which, among other things, the release of active substance of highly concentrated delayed-action medicinal forms can be regulated without changing the basic formulation.

The method in accordance with the invention makes possible the intimate, thorough mixing of the substances to be granulated, from which a particularly homogeneous distribution of the contents in the resulting granulate results. By means of the introduction of gas, provided for in accordance with the invention, into the granulation mass formed, a desired porosity can be imparted to the latter, so that it is possible with the method in accordance with the invention to influence the release of pharmaceutical active substances contained in the granulates from the final medicinal forms, for example tablets.

CLAIMS

1. Method for the production of granulates comprising at least one pharmaceutical active substance, comprising the bringing of the powder or powder mixture to be granulated into an extruder, the addition of granulation fluid for the formation of a granulation mass and the compacting of the granulation mass.

2. Method as in claim 1,
characterized by the fact that after the compacting of the granulation mass a gas or gas mixture is passed into the granulation mass.

3. Method as in claims 1 or 2,
characterized by the fact that for the dosaging of the powdered starting material a gravimetric metering screw is used.

4. Method as in one of the preceding claims,
characterized by the fact that a cellular wheel charging valve is used to bring the powder into the extruder.

5. Method as in one of the claims 2-4,
characterized by the fact that the gas passed into the granulation mass is nitrogen.

6. Method as in one of the preceding claims,
characterized by the fact that the granulate produced is furthermore screened and/or dried and/or mixed with additional components.

7. Device for the production of granulates comprising at least one pharmaceutical active substance, comprising an extruder and a device for the dosaging of the powder or powder mixture to be granulated.

8. Device as in claim 7, furthermore comprising a device for introduction of the fluid required for the granulation.

9. Device as in claim 7 or 8, furthermore comprising a device for the introduction of a gas into the granulation mass.

10. Granulate comprising at least one pharmaceutical active substance, produced by means of a method according to one of the claims 1-6.

11. Pharmaceutical composition comprising a granulate in accordance with claim 10.

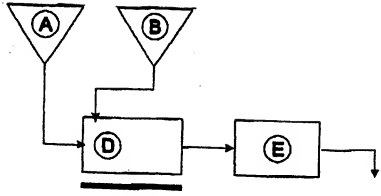

Figure 1

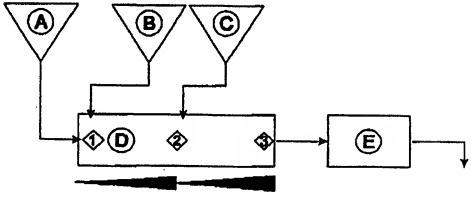

Figure 2

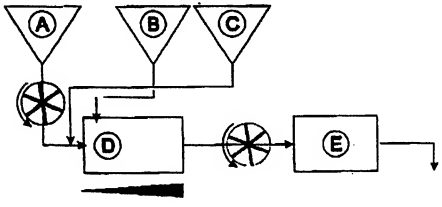

Figure 3

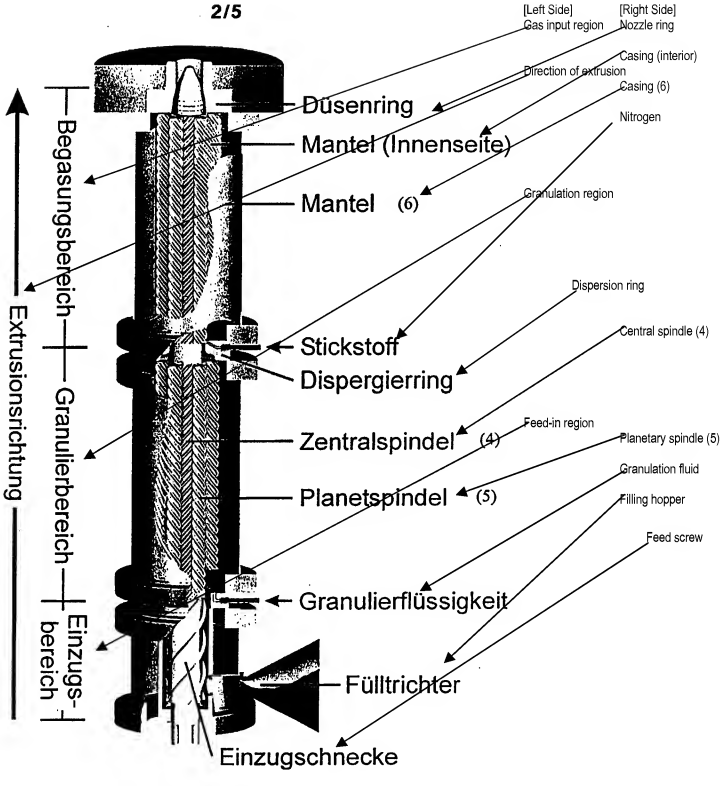
[Left Side]
Gas input region
[Right Side]
Nozzle ring
Casing (interior)
Direction of extrusion
Casing (6)
Nitrogen
Granulation region
Dispersion ring
Central spindle (4)
Feed-in region
Planetary spindle (5)
Granulation fluid
Filling hopper
Feed screw
Düsenring
Mantel (Innenseite)
Mantel (6)
Stickstoff
Dispergierring
Zentralspindel (4)
Planetspindel (5)
Granulierflüssigkeit
Fülltrichter
Einzugschnecke
Begasungsbereich
Granulierbereich
Einzugs-bereich
Extrusionsrichtung

Figure 4

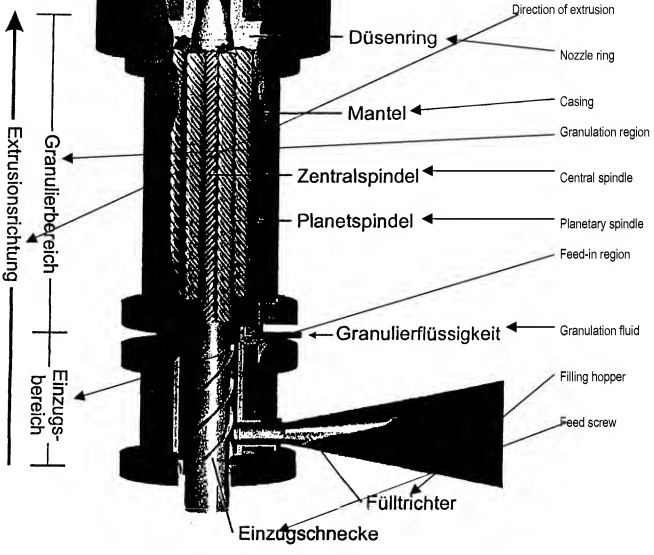
Direction of extrusion
Düsenring
Nozzle ring
Mantel
Casing
Granulation region
Zentralspindel
Central spindle
Planetspindel
Planetary spindle
Feed-in region
Granulierflüssigkeit
Granulation fluid
Filling hopper
Feed screw
Fülltrichter
Einzugschnecke
Extrusionsrichtung
Granulierbereich
Einzugs-bereich

Figure 5

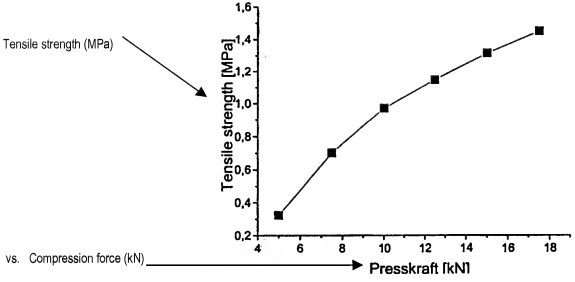

Figure 6

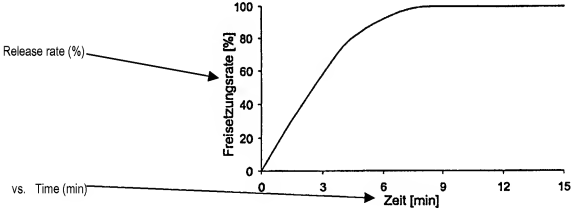

Figure 7

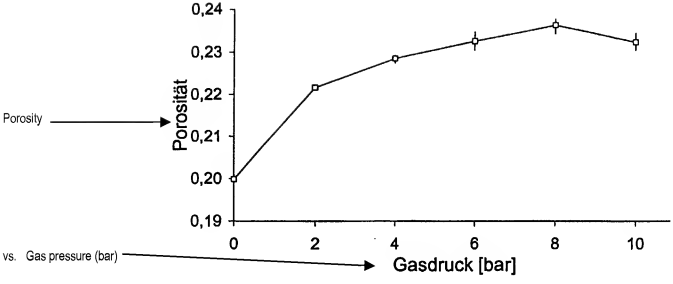

Figure 8

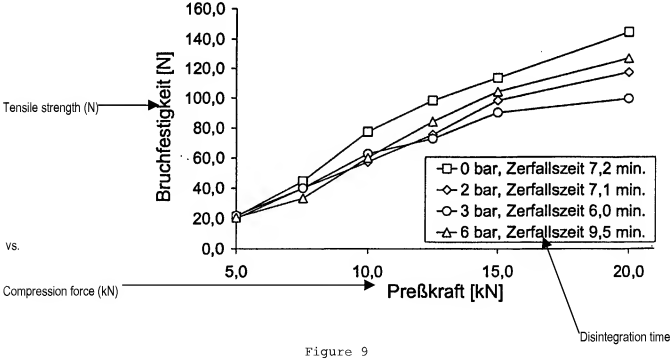

Figure 9